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Review Article

Aging and Injury: Alterations in Cellular Energetics and Organ Function

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ABSTRACT: Aging is characterized by increased oxidative stress, heightened inflammatory response, accelerated cellular senescence and progressive organ dysfunction. The homeostatic imbalance with aging significantly alters cellular responses to injury. Though it is unclear whether cellular energetic imbalance is a cause or effect of the aging process, preservation of mitochondrial function has been reported to be important in organ function restoration following severe injury. Unintentional injuries are ranked among the top 10 causes of death in adults of both sexes, 65 years and older. Aging associated decline in mitochondrial function has been shown to enhance the vulnerability of heart, lung, liver and kidney to ischemia/reperfusion injury. Studies have identified alterations in the level or activity of factors such as SIRT1, PGC-1α, HIF-1α and c-MYC involved in key regulatory processes in the maintenance of mitochondrial structural integrity, biogenesis and function. Studies using experimental models of hemorrhagic injury and burn have demonstrated significant influence of aging in metabolic regulation and organ function. Understanding the age-associated molecular mechanisms regulating mitochondrial dysfunction following injury is important towards identifying novel targets and therapeutic strategies to improve the outcome after injury in the elderly.

Key words: aging, hemorrhage, ischemia, mitochondria, sirt1, hypoxia

Aging is an inevitable natural phenomenon wherein there is a gradual decline in the physical and mental faculties of an individual. Since the founding of National Institute of Aging in 1974, there has been a concerted effort to address questions on the biology and epidemiology of aging to extend the healthy active years of life. With the availability of antibiotics and vaccines, together with major health research commitment in developed countries, the world has witnessed tremendous improvement in human health and average life expectancy in the past century [1, 2]. In 2010, there were 524 million people aged 65 years and older worldwide and the number is projected to be 1.5 billion by 2050[3]. Soon the elderly population is expected to outnumber children under age 5. This elder bloom is expected to have severe socio-economic impact especially in the developing countries which account for over 60% of the older population [4].

One major reason for the remarkable improvement in life expectancy is the shift in the disease prevalence from infectious/parasitic to non-communicable diseases [3]. According to the Centers for Disease Control (USA), injury is a leading cause of death in the age range 1-45 years [5]. Though injury death rate as percent of total death decreases with age, death rate due to injury sharply increases in adults aged 65 and older [5]. The incidence of diseases such as heart disease, cancer, diabetes, stroke and hypertension has been found to increase with aging. Aging also remains as a strong risk factor for neurodegenerative disorders like Alzheimer's disease [1, 6]. The current medical advances have significantly

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improved the outcome or delayed the onset of these devastating conditions. However the predicted increase in the life expectancy in the future years demands for even better healthcare and disease prevention measures. A better understanding of molecular basis of organ dysfunction with aging is essential in this regard. This review focuses on the influence of aging on the outcome following injuries with emphasis on the regulation of molecular pathways.

Aging and Injury, an Overview

Aging not only imposes a high risk for injuries, but also adversely affects clinical outcome following injuries. Trauma is among the major causes of death and disability and almost half of deaths due to trauma are due to hemorrhage or its consequences [7]. Aging enhances the risk for brain injury after intracellular hemorrhage and ischemic/reperfusion (I/R) injury in various organs such as heart, liver, lungs, and kidney [8-14]. Following hemorrhagic shock, aging was reported to exacerbate tissue damage in multiple organs [15]. Shock index, defined as the ratio of heart rate to systolic blood pressure, is a useful indicator of significant injury in trauma patients [16]; nevertheless, age multiplied by shock index has been reported to be a better predictor of early mortality following injury compared to heart rate or systolic blood pressure [17].

Aging is also a crucial factor that contributes to the poor clinical outcome after burn injury. Age related medical conditions and deterioration of immune functions contribute to the delayed recovery in elderly patients after major burn [18]. Septic complications arising after burn and trauma are also influenced by aging. For instance, aged mice succumbed more easily to polymicrobial sepsis induced mortality compared with young mice due to failure in mounting an effective innate immune response [19]. Age-related immunosenescence predisposes the elderly patients to severe infections and slower recovery. According to Franceschi et al, human immunosenescence is characterized by deteriorated clonotypical immunity and a sustained innate immunity with age [20]. Several factors like altered macrophage and T-cell infiltrations into wounds, altered chemokine content and a decline in the phagocytic response of macrophages in the elderly contribute to the delayed wound repair [21].

Hypoxic and ischemic conditions following injury may further exacerbate adverse effects of aging on mitochondrial function and organ function. In this review we will give a brief overview on some of the studies demonstrating functional decline in heart, liver and brain following hemorrhage, and ischemia-reperfusion injuries with aging and discuss mitochondrial functional alterations.

Aging and Injury: Effects on Organ Function

Influence of aging on cardiac injury: Aging enhances the susceptibility of heart to damage from I/R injury [11, 22]. Declining cardioprotection with aging may be attributed to a number of factors including ionotropic regulatory mechanisms, metabolic alterations and oxidative stress influencing cell survival pathways [23, 24]. Hypoxic preconditioning was found to improve recovery of young rat hearts following ischemia by bringing down elevated Na^+ although it failed to protect aging hearts [25]. Ischemic preconditioning (IPC) was also shown to be beneficial in young healthy human subjects in limiting I/R injury induced endothelial dysfunction [26]. However IPC mediated protection was severely compromised in older subjects [26]. Studies from our laboratory have shown an age dependent reduction in cardiac performance following trauma-hemorrhage (T-H) [27]. Aging per se induces significant structural and functional changes in the cardiovascular system [28]. Significant alterations in left ventricular diastolic function has been reported with advancing age which can lead to cardiovascular diseases like ischemic heart disease and congestive heart failure [29]. An aging heart is characterized by hypertrophy or marked loss of cardiomyocytes which eventually contribute to myocardial dysfunction [30]. One of the factors contributing to cardiomyocyte apoptosis has been suggested to be age related increase in local angiotensin (Ang) II converting enzyme and concentration of Ang II in cardiac tissues [31]. Studies also show that activation of SIRT1 mimics ischemic preconditioning and protects the heart from I/R injury [32]. Decreased cardiac mitochondrial function and increased oxidative damage may be responsible for the decline in cardiac performance with age, and upregulation of mitochondrial function may restore cardiac function with aging and injury [32, 33].

Influence of aging on liver injury: Aging decreases the ability of liver to withstand trauma [34]. It has been suggested that as the liver is a highly aerobic organ, it is vulnerable to hypoxic and ischemic stress [35, 36]. It is known that liver I/R injury induces the expression of heat shock protein 70 (HSP70), but the older mice displayed much lower hepatic expression of cytoprotective HSP70 and higher levels of serum HSP70 than did younger ones [12]. Further studies by the same group demonstrated that induction of HSP70 results in a significant reduction in liver injury and was associated with a reduced liver neutrophil recruitment, liver nuclear factor-kappa B activation, and attenuated serum levels of tumor necrosis factor-alpha (TNFα) and macrophage inflammatory protein-2 [37]. Studies by Matsutani et al reported that the extent of hepatic damage following T-H is dependent on the age of the subject [38]. Hepatocytes from young and

middle aged mice subjected to T-H showed considerable differences in cytokine production and intercellular adhesion molecule 1 (ICAM-1) expression. Following T-H, expression of proinflammatory cytokines, TNFα and IL-6 in hepatocytes was significantly enhanced while anti-inflammatory cytokine IL-10 was reduced in middle aged mice, but remained unchanged in young mice, all of which together account for the extended hepatic damage in the older age group [38]. Liver undergoes an age dependent susceptibility to I/R injury due to reduction in autophagic response and an age dependent loss of autophagy related protein, ATG4B in the liver has been reported [39]. A major consequence of injury or critical illness is the development of acute insulin resistance in the liver, skeletal muscle and adipose tissue [40]. Liver insulin resistance is attributed to TNFα mediated signaling pathways whereas skeletal muscle insulin resistance occurs mainly due to elevated glucocorticoid levels, both of which result in inhibitory serine phosphorylation of IRS-1 or degradation of IRS [41].

Aging and brain injury: Studies in mouse models have clearly demonstrated that aging negatively influences the outcome following TBI due to primary injuries as well as prolonged acute edema, increased opening of the blood-brain barrier and enhanced neurodegeneration [42]. In aged mice, TBI induced significant downregulation of inwardly rectifying K(+) channel (Kir4.1) and glutamate transporter-1 (GLT-1) expression in pericontusional cortex compared to adult TBI mice. As a result, aged TBI mice underwent severe neuronal depolarization and excito-neurotoxicity [43]. The cognitive recovery of adult patients following TBI is severely impaired due to age associated decline in neurogenic response. Rats subjected to moderate fluid percussive injury revealed a slow rate of proliferation and differentiation of cells, and more glial differentiation in the dentate gyrus of hippocampus in adults post injury [44]. Another reason for the deteriorated neurogenic response is the increased apoptosis of mature neurons in the granular cell layer of dentate gyrus [45].Distinctive cellular responses in the dentate gyrus contribute to the poor cognitive recovery among the aged. Moreover, aging is associated with diffuse deposition of amyloid-beta protein in specific regions of the brain following head injury, indicative of Alzheimer's like pathology [46]. Aging also affects the regeneration of damaged axons after peripheral nerve injury which could potentially result in immobilization of the individual. The impaired regeneration is proposed to be due to slow clearance of debris by damaged nerves thus blocking the regenerating axons [47].

Aging has been demonstrated to show profound influence on all organs following injury [48-51]. Hence aging not only makes an individual more susceptible to multiple organ injuries but also worsens the outcome following injuries. ATP dependent processes are critical for cellular metabolism and an age associated decline in the function of ATP generating organelle, mitochondria, is well established [52]. Understanding the mechanisms involved in different organ injuries is essential in designing new intervention strategies to improve clinical outcome.

Aging and Injury: Effects on Mitochondrial Homeostasis

The mitochondrial free radical theory of aging first suggested by Harman in 1972 proposed accumulation of mitochondrial damage as a major driving force in the aging process. According to this theory, generation of reactive oxygen species (ROS) by mitochondrial respiratory chain increases with age and causes oxidative damage to various cellular constituents [53]. A key target of mitochondrial derived ROS is mitochondrial DNA, due to its close proximity to the respiratory chain and lack of protective histones. The increased levels of somatic mitochondrial DNA damage impair the respiratory chain function promoting further free radical production triggering a vicious cycle that result in organ dysfunction and aging phenotype [52, 53]. A large body of evidence supports the mitochondrial theory of aging suggesting an inverse relationship between free radicals and longevity of the organism [54-57]. However this theory has been questioned by some studies that show a lack of correlation of free radicals or antioxidants with life span in different species [58-61]. Apart from being the ATP factory of cells, mitochondria perform a myriad of functions like redox homeostasis, calcium storage and signaling, regulation of membrane potential, apoptosis and inflammasome activation. Therefore age dependent decline in mitochondrial function can adversely affect the cells' bio-energetic and survival mechanisms.

Mitochondrion is increasingly being recognized as a key subcellular target of age related susceptibility to injury [22, 27]. Lucas et al have shown a decline in the mitochondrial respiration during reperfusion of ischemic hearts of aged rats (24 months old) but not young hearts (8 months old) [22]. Cardiac reperfusion increases the concentration of 4-Hydroxy-2-nonenal (HNE), a product of lipid peroxidation, which is known to inhibit mitochondrial respiration in vitro by modifying and inactivating key enzymes. [22]. One of the HNE susceptible targets is alpha-ketoglutarate dehydrogenase, a key enzyme in the TCA cycle. Age dependent inactivation of alpha-ketoglutarate dehydrogenase has been implicated in reperfusion induced decline in mitochondrial respiration [62]. Additionally complex I and IV activities were also reduced during ischemia and

reperfusion respectively, which further contribute to the magnitude of respiratory damage [62]. Aging has been shown to decrease complex III activity selectively in the interfibrillar mitochondria through cytochrome c binding site alteration, with a further reduction in activity during ischemic injury [63]. During reperfusion, cardiac tissues of middle aged rats displayed higher aconitase to fumarase ratios indicative of higher mitochondrial oxidative stress [64]. The increased mitochondrial ROS production by middle aged hearts impaired the restoration of cardiac mechanical function during reperfusion [64]. Mitochondrial but not cytosolic calcium overload has been implicated in I/R injury in isolated rat hearts [65]. Cardiac mitochondrial sensitivity to calcium induced mitochondrial permeability transition pore (mPTP) opening was also increased during aging which aggravated the I/R outcome [66]. Taken together, all these studies undoubtedly prove that aging hearts sustains a greater damage during I/R primarily due to defective oxidative phosphorylation and enhanced oxidant production resulting in mitochondrial dysfunction.

Studies from our laboratory have attempted to understand how aging influences cardiac mitochondrial gene expression and cardiac function following hemorrhagic injury [27, 67]. T-H is often associated with an impaired cardiovascular function even after fluid resuscitation. Aged rats (22 months old) subjected to T-H displayed a significant reduction in left ventricular function compared to younger ones (6 months old) [27]. This effect may be primarily attributed to T-H induced tissue hypoxia which leads to generation of reactive oxygen species (ROS) and altered mitochondrial function. A significant increase in cytochrome c release (indicative of apoptosis) to the cytosol was observed following T-H in both age groups although much higher increase in aged group. A RoMitoChip developed in our laboratory was used to investigate the changes in mitochondrial gene expression (mitoscriptome) following T-H injury in aged and young rats. This chip had 419 probe sets representing mitochondrial genes and nuclear genes encoding mitochondrial proteins, from the rat. A marked difference in the gene expression profile was observed following injury, with the aged rats showing lesser number of gene alterations compared to younger ones. Following T-H, some of the genes showed similar changes in expression in both age groups. Among the genes upregulated in both age groups included MYC, HIF-1α and Sod2 and commonly downregulated included fatty acid oxidation genes like carnitine palmitoyltransferase 1 and metabolic enzymes like isocitrate dehydrogenase 1 (IDH1). IDH1 mutation is frequently found in secondary glioblastoma multiforme [68]. Since T-H induces a hypoxic environment similar to tumor microenvironment, it would be interesting to scrutinize the role of IDH1 and other genes, participating in hypoxic response, in mediating metabolic changes following injury. A large number of genes showed exclusive alterations in either age groups among which pro-apoptotic protein, Bnip3 was upregulated and PGC-1α was downregulated in 6 month old animals. In the older rats, transcripts of 12 different tRNAs demonstrated a significant upregulation implicating a potential translational regulation in the aged.

The mitoscriptome profiling using the RoMitochip led to the identification of silent mating type information regulation 2 homolog 1 (SIRT1) as a potential target in hemorrhagic injury[69]. SIRT1, a member of sirtuin family of proteins, is an NAD^+-dependent protein deacetylase which deacetylates a broad range of transcription factors, coregulators and histones thereby regulating gene expression [70]. SIRT1 activation has several cardioprotective effects like regulating oxidative stress, suppressing apoptosis and inflammation. SIRT1 is known to deacetylate and activate peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α), a coactivator of transcription factors like PPARγ, which plays a crucial role in mitochondrial biogenesis [71]. Gene expression and activity of SIRT1 was decreased following T-H implicating its role in mitochondrial dysfunction. Accordingly, two of the PGC-1α downstream targets, Nrf-1 and Foxo1 were also downregulated following T-H [72].

A recent study by Gomes et al demonstrated a disrupted nuclear-mitochondrial communication during aging due to specific decline in nuclear NAD^+ levels and hence a loss of SIRT1 activity [73]. According to the authors, SIRT1 can maintain mitochondrial homeostasis independently of PGC-1α by regulating the levels of HIF-1α which is inhibitory to mitochondrial biogenesis and respiration. SIRT1 induces von Hippel–Lindau mediated degradation of HIF-1α [73]. SIRT1 is also known to directly inactivate HIF-1α by deacetylation [74]. On the contrary, stabilization of HIF-1α reduces ability of c-MYC to bind and activate the promoter region of nuclear encoded mitochondrial transcription factor, mitochondrial transcription factor A (TFAM) [73]. Therefore decreased SIRT1 activity during aging can result in a specific decline in mitochondria-encoded but not nuclear-encoded oxidative phosphorylation (OXPHOS) genes. In this paper, Sinclair and coworkers provide evidence for a pseudohypoxic state in aging, and suggest that increasing NAD^+ levels or prevention of functional levels of HIF-1α might be useful towards delaying aging pheonotype[73]. c-MYC plays an important role in regulating mitochondrial biogenesis by inducing genes involved in mitochondrial structure and function. As previously mentioned, c-MYC activates gene transcription of TFAM, a key transcriptional regulator and mitochondrial DNA replication factor [75]. It is reported that during

pathological stress c-MYC regulates cardiac metabolism and mitochondrial biogenesis despite reduced PGC-1α activity [76]. In recent studies we found that c-MYC gene was significantly upregulated following T-H in both old and young rats. It is likely that activation of c-MYC following T-H may be cell's intrinsic adaptation machinery to protect against mitochondrial dysfunction. This may also be consistent with another study that reported a c-MYC-SIRT1 feedback loop; c-MYC binds to SIRT1 promoter to induce its transcription whereas SIRT1 deacetylates c-MYC reducing its stability [77]. These findings implicate multiple mechanisms of SIRT1 mediated c-MYC regulation. HIF-1α has also been shown to inhibit c-MYC activity by binding and activating gene transcription of the c-MYC repressor, MXI-1 and by promoting proteosome dependent degradation of c-MYC [78]. HIF-1α gene was significantly upregulated following T-H in both young and old rats [27]. Augmentation of oxygen sensing transcription factor HIF-1α expression promotes a shift in the metabolism to glycolytic pathway and concomitant reduction in oxidative phosphorylation.

According to a recent study, aged heart is more vulnerable to I/R injury due to impaired aldehyde dehydrogenase (ALDH2) activity and therefore increased aldehyde/carbonyl stress and concomitant reduction in SIRT1 activity [79]. Pharmacological ALDH2 activation was able to restore cardiac SIRT1 activity by decreasing carbonyl stress [79]. SIRT1- PGC-1α axis was also found to be important in maintaining mitochondrial function in podocytes and suppression of SIRT1 by cellular stress leads mitochondrial dysfunction triggering podocyte injury paving way to glomerular sclerosis [80]. Based upon the studies in animal models it may be speculated that targeting SIRT1 may provide therapeutic alternatives to improve clinical outcome after injury in the aged [81].

Age associated molecular changes occurring in the intracellular compartments affect the cellular responses and organ function at times of various insults. It is important to understand the molecular mechanisms regulating differential response of young and aged tissues to injury. Systematic elucidation of the mechanistic details would help design novel treatment strategies to overcome the deleterious effects of aging on injury outcome. In addition to mitochondrial dysfunction other inter-related biological process such as altered ER stress response, apoptosis and autophagy are also major determinants of impaired tissue injury response. Hence studies targeting these processes are also expected to yield useful information in understanding injury response and to devise better methods to restore organ function.

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